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59

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/046,530	01/14/2002	Scott P. Bruder	640100-440	5553
27162	7590	03/29/2004	EXAMINER	
CARELLA, BYRNE, BAIN, GILFILLAN, CECCHI, STEWART & OLSTEIN 5 BECKER FARM ROAD ROSELAND, NJ 07068			SHUKLA, RAM R	
			ART UNIT	PAPER NUMBER
			1632	

DATE MAILED: 03/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b> 10/046,530	<b>Applicant(s)</b> BRUDER ET AL.	
	<b>Examiner</b> Ram R. Shukla	<b>Art Unit</b> 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☐ Responsive to communication(s) filed on \_\_\_\_.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-19 is/are pending in the application.  
4a) Of the above claim(s) \_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-19 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 14 January 2002 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. ____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date ____. | 6) <input type="checkbox"/> Other: ____.  |

### **DETAILED ACTION**

1. Claims 1-19 are pending.
2. Instant application is a continuation of 09/314,855, now US Patent 6,355,239 which claims priority to 09/039,127 filed March 13, 1998.

### ***Double Patenting***

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

3. Claims 11-16 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 6,355,239 B1. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 11-16 of the instant application recite a method for promoting muscle tissue growth that would encompass a method of promoting connective tissue growth, the invention of claims 1-12 of the 6,355,239 B1 patent.

### ***Claim Rejections - 35 USC § 112***

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-10 and 17-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 11-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a human subject for promoting connective tissue growth by administering allogeneic mesenchymal stem cells, does not reasonably provide enablement for a method for treating by promoting the growth of any muscle tissue. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)).

Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore

skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The invention of claims 1-10 encompasses method of promoting hematopoietic or progenitor cell engraftment in an animal by administering non-autologous mesenchymal stem cells (MSC). Dependent claims limit the cells to allogeneic, animal to a human, that the cells are not MHC matched, the MSC are free of blood, different routes of administration and that the MSC express incorporated genetic material. Claims 17-19 recite promoting connective tissue implantation by adhering allogeneic MSC onto connective surface of a prosthetic device. The method encompasses human treatment. Claims 11-16 encompass method of treating a human subject for promoting growth of any muscle by administering allogeneic MSC.

The specification as filed describes that MSC are invisible to the immune system and that they actively reduce the allogeneic T cell response (see page 3). The specification also teaches allogeneic canine study where there is bone growth when allogeneic MSCs were transplanted in contralateral thigh (see page 24). The specification does not provide any working examples of treating any human or any animal where hematopoietic or progenitor cell engraftment is enhanced by MSC transplantation. Additionally, the specification does not teach any working examples as to whether any muscle tissue growth can be promoted by administering allogeneic MSC. With respect to a method in a human, the specification does not provide any working examples. It is noted that claims recite practicing methods in a human, however, any specific description and guidance is not provided for practicing the method in a human.

Claim 1 encompasses transplantation of non-autologous transplantation that would encompass transplantation of xenogeneic cells. However, at the time of the invention, transplantation of any xenogeneic cells was not routine as discussed below. Fred Gage (Nature 392:18-24, 1998) noted that for non-autologous cells, the most serious challenge is the destruction of cell implant by the host's immune system and that in xenografts, complement mediation is the major problem whereas the hyperacute rejection is the rapid and dramatic immunological

Art Unit: 1632

response. The specification does not teach how to address the issues of hyperacute and complement mediation associated with the xenotransplantation of cells.

At the time of the invention, xenogeneic transplantation of any cells was not routine. Samstein et al (Samstein et al. Journal of American Society of Nephrology 12:182-193, 2001), reviewing the state of the art of physiologic and immunologic hurdles of xenotransplantation, summarized:

“Although the potential advantages of xenotransplantation generate enthusiasm, these advantages must be weighed against what may seem to be the daunting hurdles to the clinical application of xenotransplantation. These hurdles include the immune response of the recipient to the transplant, the physiologic limitations of the transplant, infection, and ethical concerns”.

In summary at the time of the invention, the art of xenotransplantation was unpredictable and the specification does not provide any guidance how to address the issues of unpredictability in xenotransplantation of MSC. It is emphasized that the specification does not provide any guidance as to how the xenotransplantation of MSC will be carried out.

The art of treating any condition with MSC was unpredictable at the time of the invention and even afterwards. In reviewing the state of the art of Marrow Stromal Stem cells, Bianco et al (The Journal of Clinical Investigation 105:1663-1668,2000) noted the plastic properties of stromal cells but cautioned that the plasticity of marrow stromal cells was not acknowledged outside the field of skeletal biology which would indicate that the use of stromal cells for any other purpose was controversial and therefore unpredictable (see left column on page 1665). Additionally, these authors recognized three clinical uses that have benefits and inherent problems- reconstructing localized skeletal defects, where a prosthetic device could be theoretically produced with culture cells –however, the authors noted that it was theoretical which indicates that it was an idea but the method was not routine at the time of the review (2002). It is emphasized that the instant application was filed in 1998 and does not provide any specific directions for practicing the claimed methods- such as to adhering MSC to prosthetics, etc. The authors further cautioned that a more difficult challenge was transduction with high

Art Unit: 1632

enough efficiency and that the proper regulation of the expression of a desired gene was problematic and in vitro results in non-human cells could not be reproduced in human cells in vitro. Furthermore, authors indicated reconstitution of some or all of the skeletal system to cure systemic diseases of the bone as most ambitious (see the last two full paragraphs in the left column on page 1666), which again indicated that unpredictability of the art. The authors further noted that stromal cells could not be systemically transplanted like hematopoietic stem cells (see the right column on page 1666 continued on page 1667). In summary, Bianco et al clearly indicates that the art of using MSC for human treatment and for treating any disease or condition was not routine and unpredictable in 2000. It is reiterated that the specification does not provide any guidance which would have corrected the deficiencies or unpredictability raised by Bianco et al.

Similar question of the suitability of MSC transplantation was raised by Minguell et al (Experimental Biology and Medicine 226:507-520, 2001) and that it was yet to be established whether the ex vivo expanded MSC competent to sustain both long term and short term mesengensis (see pages 514-515, particularly page 515). In conclusion, at the time of the invention, it was not routine to promote the growth of muscle or promote hematopoietic cell engraftment and the specification does not provide any specific teaching as to how to practicing the claimed methods commensurate with the scope of the claims.

Therefore, in view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, an artisan of skill would have required extensive experimentation to practice the claimed invention. It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991).

### ***Claim Rejections - 35 USC ' 103***

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

Art Unit: 1632

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

7. Claims 11-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Caplan and Haynesworth (Caplan AI and Haynesworth SE. US Patent No. 5,226,914 dated 7-13-1993.) in view of Bruder et al (Bruder SP et al. J. Cell. Biochem. 56:283-294. 1994), Nevo Z., et al. (Nevo Z., et al. Cell Transplantation 7(1) 63-70, 1998) , Robinson et al (Robinson D et al. Agents Actions Suppl 39:231-235. 1993 (abstract)), Stiller et al (Stiller CR et al. N Engl. J. Med. 294:978-982. 1976) and Kessinger (Kessinger A J Clin. Apheresis 5:97-99. 1990 (Abstract)), in view of Theobald et al (Transplantation 55:128-133, 1993).

Caplan and Haynesworth teach a method of treating skeletal and other connective tissue disorders in humans utilizing isolated and culturally expanded marrow-derived mesenchymal stem cells (see the abstract and example 2). In col 3 (lines 21-34), they state that the marrow derived mesenchymal cells can differentiate into bone, cartilage, and various types of connective tissue. They also provide methods for, the isolation and purification of mesenchymal stem cells, culture to expand to larger quantities, and their application for connective tissue repair (see examples and claims in columns 9-20). Caplan and Haynesworth also teach that mesenchymal stem cells can be used for augmentation of marrow transplantation (enhancement of hematopoietic stem or progenitor cell engraftation)(see lines 46-68 in col 16 continued in col 17 lines 1-30). This prior art does not teach the method to use allogeneic mesenchymal stem cells for treatment of a patient that needs such a treatment.

Bruder et al. review the steps of bone development, steps of mesenchymal stem cells into its different lineages, and the use of mesenchymal stem cells (MSC) for the repair of bone and skeletal regeneration therapy (see the abstract and figures 1 and 2). Figure 4 shows that cartilage tissue is formed from MSC and

Art Unit: 1632

cartilage cells after several steps of differentiation lead to the formation of mature bone.

Nevo Z., et al. teaches regeneration of skeletal tissues by grafting allogeneic limb bud mesenchymal stem cells in chicken.

Robinson et al teach that the regeneration of destroyed articular cartilage can be induced by transplantation of fetal allogeneic and autogeneic cartilage cells into the defects (see the abstract).

Stiller et al teach that humoral and cellular immune response have a decisive role in the acceptance or rejection of allogeneic grafts (see lines 1-3 of the introduction on page 978). They also teach that anti-donor immune response can be used for the prediction of transplant rejection of tissues and that the cell-mediated lymphotoxicity was the best predictor of rejection (see abstract). They further teach the method to assay anti-donor immune response in tissue transplants using the mixed lymphocyte reaction (see methods section on page 979).

Kessinger review clinical results on autologous transplantation of peripheral blood stem cells. He teaches that autologous hematopoietic stem cells are infused intravenously in patients following marrow-lethal cancer therapy (see abstract).

Theobald et al teach that certain cultured human cells, that include human dermal fibroblasts, human smooth muscle cells, and human epidermal cells, do not elicit allogeneic stimulation or they may function as "neutral allografts". They further add, " it appears that certain cells lack as-yet-undefined costimulatory factors required for their effective recognition as foreign. These results support the notion that cultured human fibroblasts, smooth muscle cells and epidermal cells could serve as building blocks of engineered "neutral allografts" for use across MHC barriers" (see abstract on page 128, col 1 and 2). They also teach that tissue engineering techniques have been applied to the fabrication of organs using cultured parenchymal and mesenchymal cells and extracellular matrix ( last para in col 2 on page 128 continued in first para in col 1 on page 129). They further note that assessment of the immunogenicity of cultured parenchymal and mesenchymal

Art Unit: 1632

cells, their expression of MHC class II and the various costimulatory factors they produce is an essential prerequisite for the fabrication of neural allografts (see last para of introduction section on page 129, in col 1, last 4 lines

At the time of the invention it would have been obvious to one of ordinary skill in the art to isolate mesenchymal stem cells from donors, purify them, test their allogeneic stimulation property and use them for treatment of damaged tissues of mesenchymal origin that include bone, cartilage, skeletal tissue, and stroma, with reasonable expectation of success because the prior art teaches all these techniques and steps thereof. The artisan would have been motivated to use the alloegenic cells for transplantation because allogeneic mesenchymal stem cells were successfully used in supporting bone growth in chicken limb buds and because mesenchymal stem cells would have been better in tissue damage repair compared to differentiated mesenchymal cells because they could differentiate in all the cells of mesenchymal lineage as taught by Bruder et al (see figure 4 in Bruder et al).

With regard to the route of administration of the mesenchymal stem cells to patients, it is noted that it would have been obvious to one of ordinary skill in the art to administer mesenchymal stem cells intravenously to an individual in need of such cells because intravenous administration of stem cells is a commonly used route for administration of marrow cells to patients who need augmentation of their hematopoietic system, for example following marrow lethal cancer therapy as taught by Kessinger et al.

4. Claims 1 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Caplan and Haynesworth , Bruder et al, Nevo et al, Robinson et al, Stiller et al, Theobald et al, and Kessinger as applied to claim 1-14 above, and further in view of Gerson et al (US Patent No. 5,591,625, dated 1-7-1997, filing date 11-24-93).

Teachings of Caplan and Haynesworth , Bruder et al, Robinson et al, Stiller et al, and Theobald et al have been described previously. None of these prior arts

Art Unit: 1632

teach to make allogeneic mesenchymal stem cells that are capable of expressing incorporated genetic material of interest.

Gerson et al teach a method to make mesenchymal stem cells that carry within them genes of interest particularly for the expression of physiologically or pharmacologically active proteins or for use in gene therapy. They also teach that these cells can be used for both in vitro or in vivo gene transfer (see example 3).

At the time of the invention, it would have been obvious to one of ordinary skill in the art to transduce a gene of interest in purified mesenchymal stem cells (that have been checked for immune reactivity) as taught by Gerson et al and use these cells in treatments as taught by Caplan and Haynesworth and Bruder et al with reasonable expectation of success because Gerson et al teach the steps of the gene transduction whereas Caplan and Haynesworth and Bruder et al teach the method of purification and use of the cells in treatment of bone diseases or other related diseases. An artisan would have been motivated to transduce the mesenchymal cells with a gene of interest because this can be used to stimulate the proliferation of the mesenchymal cells at the site of injury by delivery of genes for cytokines or other growth factors as taught by Gerson et al (see col 8).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (571) 272-0735 . The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached at (571) 272-0804. The fax phone number for TC 1600 is (703) 703-872-9306. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the William Phillips whose telephone number is (571) 272-0548.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR

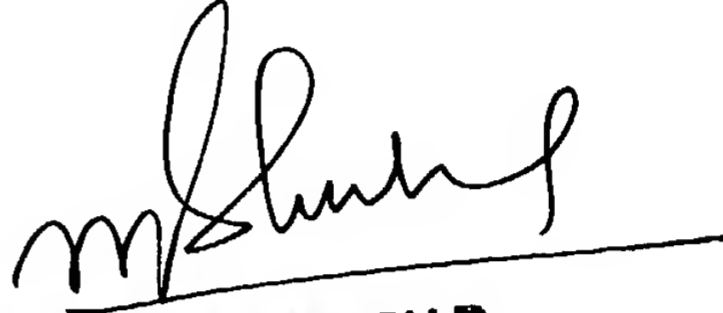
Application/Control Number: 10/046,530

Page 11

Art Unit: 1632

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Ram R. Shukla, Ph.D.  
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**RAM R. SHUKLA, PH.D.  
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